



## Guest Editorials

## Type III hereditary angioedema: defined, but not understood

Type III hereditary angioedema (HAE) is a familial form of angioedema in which complement C4 and C1 inhibitor (C1 INH) protein and function are normal.<sup>1,2</sup> Most patients are women, although an occasional male is identified, and a close association with estrogen as a precipitant of attacks of angioedema is seen (contraception, postmenopausal symptom control), beyond that noted for types I and II HAE. Like types I and II HAE, angioedema is recurrent, it is not associated with urticaria, and it is unresponsive to antihistamines or corticosteroids. These properties define the disorder, but we do not have a test that can be used to make the diagnosis, and the pathogenic mechanism(s) by which swelling is produced are uncertain. Overproduction of bradykinin is assumed, but not proven, yet many published observations support that conclusion. Attacks of swelling last many days and can include episodes of laryngeal edema or severe gastrointestinal symptoms, all of which are typically seen when bradykinin is the mediator (eg, types I and II HAE; angioedema due to angiotensin-converting enzyme inhibitors). A mutation in factor XII, exon 9 consisting of either Thr 309 lys or Thr 309 arg<sup>3</sup> has been associated with type III HAE patients, and, although specific for this disorder, it is found only in 25 to 30% of patients whose swelling is unexplained but is clearly familial. The mutation was reported to cause excessive conversion of prekallikrein to kallikrein<sup>4</sup> and was described as a “gain of function” mutation. This designation is misleading because such a mutation might render the activated factor XII resistant to the action of C1 INH, with the specific activity of the factor XIIa being normal. Biochemical semantics notwithstanding, a publication soon thereafter attempted to verify this mechanism and found no evidence of enhanced activation of the factor XII-prekallikrein-bradykinin forming cascade.<sup>5</sup> Thus, if the factor XII mutation causes abnormal production of bradykinin, we do not know how or why that occurs. Estrogen is known to raise levels of factor XII<sup>6</sup> and depress levels of C1 INH<sup>6</sup> and bradykinin-degrading enzymes such as aminopeptidase P and angiotensin-converting enzyme.<sup>7</sup> This would contribute to elevated bradykinin levels if the cascade were activated but are not sufficient to explain the occurrence of severe episodes of angioedema. For example, idiopathic angioedema in women is not estrogen dependent and not obviously estrogen sensitive.

The article by Marcos et al<sup>8</sup> in this issue describes their findings in 29 patients with type III HAE. Twenty-two of the 25 female patients demonstrate a strong association with estrogen, and baseline C4 and C1 INH levels were normal. This is consistent with expectations based on prior publications, as is the occurrence of gastrointestinal attacks in 9 patients and laryngeal edema in 5. One rather extraordinary finding is that all 29 patients had the Thr 309 lys mutation in the factor XII gene. They also observed that the C1 INH level in some patients dropped below the 50% mark during attacks or did so during preg-

nancy. Perhaps this indicates consumption of the inhibitor by proteases activated during attacks of swelling, which would again suggest activation of enzymes involved in bradykinin formation (factor XIIa, factor XII, kallikrein) or activation of C1.<sup>9</sup>

This manuscript provides valuable information regarding the clinical presentation of type III HAE patients. Three of the patients reported had no family history, but the presentation suggested type III HAE, and the presence of the factor XII mutations confirmed the diagnosis. This raises an issue regarding use of this genetic test as a screening test for patients with recurrent angioedema in the absence of urticaria where the diagnosis is not obvious. I would argue against use of the assay in this fashion because the uncertainty of what is being seen is so great. For types I and II HAE, 25% of patients present initially with no family history but are diagnosed by quantitating C4 and C1 INH by protein and function.<sup>10</sup> The absent family history may indicate that the proband has a new mutation or that the history is unreliable. This might also be true for type III HAE, but we have no such assay. Overall the factor XII mutations are found in a minority of patients even when there is a family history. What percentage positive is likely when there is no family history, considering that idiopathic angioedema is far more common? I suspect that very few positives would be obtained. One could argue that the nonhistaminergic subpopulation of patients with idiopathic angioedema (ie, those refractory to prophylaxis with high-dose antihistamines) would be the ones to study, and I would agree if a research project to ascertain the incidence of type III HAE within this population were proposed. Marcos et al<sup>8</sup> diagnosed type III HAE in a few patients thought to be within this subpopulation of patients with idiopathic angioedema and also found asymptomatic relatives with the same mutation. Several questions remain open. While an occasional patient with type III HAE might be diagnosed in this manner, how many type III patients lack the mutation, and how many have a completely different disorder, and how is antihistamine resistance defined? Evidence of a factor XII mutation in patients with recurrent angioedema of unknown origin should be sought only if a family history is clear.

Type III HAE is a relatively new disorder and, although it is uncommon, further research is needed to understand its pathogenic mechanism and to develop a diagnostic assay. Appropriate treatment modalities will then follow, and any effort should shed light on other forms of angioedema that are more commonly seen, but equally enigmatic.

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## Is nerve growth factor involved in the symptoms of rhinitis?

Patients suffering from rhinitis soon tire of the relentless nasal itching, rhinorrhea, sneezing, and nasal blockage. Whether the rhinitis is atopic in nature or idiopathic, the panoply of troubling symptoms remains constant. These symptoms, as a whole, speak directly to disease mechanism. The symptoms of rhinitis are what one would expect if there were inappropriate activity in the trigeminal afferent (sensory) nerves innervating the nasal mucosa. Activation of these nerves would likely lead to itching, sneezing, cholinergic reflex secretions (rhinorrhea), and vasodilation (nasal blockage). The questions remain: What alters the trigeminal nervous system in rhinitis, and are the mechanisms the same between the 2 seemingly disparate disorders of allergic rhinitis and nonallergic idiopathic rhinitis?

In a recent issue of *The Journal*, Gelincik et al<sup>1</sup> evaluated the number of mast cells and nerve growth factor (NGF) expressing cells in nasal biopsy specimens of patients with symptomatic allergic rhinitis or symptomatic idiopathic rhinitis, and in nonsymptomatic controls. They describe a striking 30-fold increase in the number of tryptase-positive mast cells in nasal biopsy specimens of those suffering from rhinitis, with some 60% of these mast cells expressing NGF. A key finding is that although the NGF-expressing mast cells in the rhinitis subjects far exceeded those in biopsy specimens taken from healthy volunteers, no difference was found between allergic and idiopathic rhinitis.

Nerve growth factor is the prototypical neurotrophin, the discovery of which led to award of the 1986 Nobel Prize in Medicine to Stanley Cohen and Rita Levi-Montalcini. NGF is a powerful growth factor that regulates growth and survival of autonomic and sensory neurons that express the high-affinity NGF receptor tyrosine kinase receptor A (TRKA). In more recent years, NGF has also been recognized to regulate the activity of many immune and structural cells, including those in the airway wall, in a manner that can contribute to the orchestration of the inflammatory response.<sup>2,3</sup>

The ability of NGF to regulate neuronal activity is not limited to periods of prenatal development. After development, interactions of NGF with its receptor (TRKA) on nerve terminals can lead to profound neuroplasticity. This is because the NGF-TRKA receptor complex is internalized and transported back to the cell body (in this case situated in the trigeminal ganglion, and possibly parasympathetic ganglion neurons), where it can alter the transcription of many relevant genes.<sup>4</sup> NGF released from the nasal mast cells could conceivably increase axonal sprouting and modulate the expression of sensory neuropeptides, activating ion channels such as the capsaicin receptor TRPV1, as well as modulatory ion channels including voltage gated sodium channels.<sup>5–8</sup> That both allergic and idiopathic rhinitis are typified with an increase in NGF-expressing mast cells might explain the observation that among structural differences between allergic and nonallergic rhini-

tis, in both disorders the nasal mucosa is hyperinnervated with substance P and calcitonin gene related peptide containing sensory nerve fibers.<sup>9</sup>

One might envisage a scenario in which mast cell activation in the nasal mucosa of subjects with allergic or idiopathic rhinitis leads to the release of mast cell mediators such as histamine and leukotriene D4 that can acutely stimulate the nearby nasal trigeminal sensory nerves, causing overt sensory nerve activation.<sup>10</sup> Based on the findings of Gelincik et al<sup>1</sup> and others,<sup>11</sup> mast cell activation also may lead to the release of neurotrophins such as NGF that can regulate the inflammatory response and uniquely lead to phenotypic changes in the sensory innervation such that the nerves respond more strongly to noxious stimuli and also respond to stimuli that healthy individuals would find innocuous. Such neuroplasticity may contribute to the “hypersensitive” state that is so often present in these individuals.<sup>12</sup>

Drugs capable of interfering with the NGF-TRKA axis are reported to have remarkable efficacy in inhibiting certain types of inflammatory pain.<sup>13</sup> Ultimately it will be left to clinical pharmacologists to determine whether the NGF-TRKA axis is pivotal in regulating the itching, sneezing, rhinorrhea, and the hypersensitive state that characterizes allergic and nonallergic rhinitis.

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